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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/600,060	07/10/00	WILLIAMS N	CTH-03

EXAMINER	
HUYNH, P	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/600,060	Applicant(s) WILLIAMS ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24,26-30 and 40-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24,26-30 and 40-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The numbering of claims is not in accordance with 37 CFR 1.126. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claims 45 to 50 have been renumbered as claims 44-48, respectively.

2. Claims 20-24, 26-30 and 40-48 are pending.

3. In view of the amendment filed 8/27/01, only the following rejections remain.

4. Claims 20-24, 26-30 and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the same reasons set forth in Paper No 7.

Applicants' arguments filed 8/27/01 have been fully considered but are not found persuasive. Applicants' position is that (1) the claim has been amended in response to this rejection wherein the amended claim 20 refers to mutants and derivatives of CtxB, Etx, and EtxB which display the parametric changes as recited in the claim; (2) dependent claim 22 is not limited to any GM-1 biding agent but only to those derivatives of Ctx, Etx or EtxB; (3) the term "modulates" has been retained in part (b) of claim 20 to define the parametric changes in IgE levels and associated Th2 cytokines levels such as IL-4 levels; (4) the term "ganglioside associated activity" has been defined on page 15, lines 7-9; (5) the agents now defined functionally in claim 20 with respect to their specific effects on IgE antibody levels and Th2 cytokines levels such as IL-4 levels does not fall within the scope of the term "agent" and accordingly, the EtxB mutant such as G33D does not demonstrate said effect.

However, amended claim 20 recites an assay method for identifying an agent useful in the treatment of an allergic or hypersensitivity condition comprising: (a) contacting a test agent with a ganglioside receptor, wherein agent is not coupled to an antigen, (b) determining whether the agent modulates a ganglioside associated activity by measuring a change in at least one parameter selected from the group consisting of a suppression in antigen specific IgE levels, or a reduction in the production of Th2 associated cytokines or a change in antigen specific T-cell

reactivity, or a change in IgG levels or a change in IgA levels or any combination thereof and (c) identifying the useful agent by observation of modulation of ganglioside associated activity. The amended claim 20 does not refer to mutants and derivatives of CtxB, Etx, and EtxB. Furthermore, the test agent as recited in claim 20 that modulates a ganglioside associated activity is determined by measuring any one parameter and said parameter does not have to be suppression of IgE, or a reduction in IL4 levels as written. Furthermore, there is insufficient written description about the structure associated with function of any mutants or derivatives of CtxB, Etx, and EtxB that bind to GM1 for a method of identifying an agent that would be useful in the treatment of an allergic or hypersensitivity condition. The specification discloses only one EtxB mutant (G33D) (See page 34, lines 19). There is no additional species of mutants or derivatives of any CtxB, Etx or EtxB. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

With regard to "a change in antigen specific T-cell reactivity or a change in IgG levels or a change in IgA levels or a combination thereof" for a method of identifying an agent that would be useful in the treatment of an allergic or hypersensitivity condition, there is insufficient written description about the change of any reactivity or levels mentioned associated with allergic or hypersensitivity condition since a change can be either increase or decrease.

Regarding "ganglioside associated activity", the specification on page 15 defines the term "ganglioside associated activity" which includes any one or more of modulating or immunomodulating a ganglioside receptor, modulating any signaling event prior to, during or subsequent to ganglioside receptor binding. The specification fails to define what essentially is the "ganglioside associated activity" based on the above definition. Furthermore, the term "modulating" can be stimulatory as well as inhibitory and they are mutually exclusive.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

5. Claims 20-24, 26-30 and 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons of record set forth in Paper No 7.

The recitation of "ganglioside associated activity" is indefinite and vague. The term "ganglioside associated activity" as defined on page 15 of the specification includes "any one or

more of modulating or immunomodulating a ganglioside receptor, modulating any signaling event prior to, during or subsequent to ganglioside receptor binding". One of ordinary skill in the art cannot appraise the metes and bound of the claimed "ganglioside associated activity" as defined. Although applicants have amended claim 20, the "ganglioside associated activity" such as a change in antigen specific T-cell reactivity, a change in IgG levels, a change in IgA levels or any combination thereof is not defined since "a change" in the levels can be either increase or decrease.

The recitation of "modulates" is indefinite and ambiguous since the direction of change can be positive or negative, while the term "modulates" can be stimulatory or inhibitory and none of these terms are defined in the specification.

6. Claims 20-24, 26-30 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nashar *et al.* (of record, Proc. Natl. Acad. Sci USA 93: 226-230, PTO 1449; see entire document) in view Yamamoto *et al.* (of record, J. Exp. Med. 185(7): 1203-1210, 1997, PTO 892; see entire document) and Kim et al (of record, J Immunology 160: 1198-1203, 1998, PTO 892; See entire document) for the same reasons of record set forth in Paper No 7.

Applicants' arguments filed 8/27/01 have been fully considered but are not found persuasive. Applicants' position is that (1) the rejection is based on a hindsight reading of the references; (2) Nashar et al teach ExtB and EtxB mutant (G33D) which cause an increase in the activation of CD4+ T cells, an increase in IL-2, IFNγ and no IL-4, IL-5 and IL-10 could be detected in the lymphocyte culture; (3) Nashar *et al* suggest that commercial preparations of Ctx and CtxB or purified CtxB are strongly inhibitory of lymphocyte proliferation (See page 229, right column); (4) Nashar et *al do* not disclose or suggest that either Ctx, CtxB, Etx or EtxB might play a role in an allergic response; (5) the specific changes/modulating in cytokine/antibody levels which occur in an allergic response and/or (6) how an assay method might be develop to identify an agent which could induce specific changes; (7) the teachings of Yamamoto *et al* are silent about the possible effects of the CtxB subunit although the Ctx triggers a Th2 dominated response to added antigens whereas Etx (LT) gives a more balanced response involving stimulation of Th1 and Th2 responses; (8) a detoxified Ctx is not the same as a CtxB subunit because even though a detoxified Ctx will not have ADP-ribosylation properties, a detoxified Ctx subunit will have other properties and (9) Kim et al refers to the cholera toxin (Ctx) and the cholera toxin B subunit (CtxB) and no mention is made of Etx or EtxB.

In response to applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Nashar *et al.* teach an assay method for identifying an agent that modulates the immune response comprising contacting a test agent such as EtxB or EtxB mutant (G33D) from the heat-labile enterotoxin of *E Coli* with a ganglioside receptor such as GM1 wherein the agent is not coupled to an antigen (See page 227, Ezyme-linked Immunosorbent Assays (ELISAs, Fig 1, in particular), determining whether said agent modulates ganglioside associated activity by measuring a change in at least one parameter such as a change in IgG or IgA levels (See Fig 2, in particular) or a change in antigen specific T-cell reactivity (lymphocyte proliferation in the presence of EtxB or EtxB mutant (G33D) (See page 228, Table 1, Fig. 3, in particular) or a change in the cytokine levels such as IL-2, IFNγ which are Th1 associated cytokines that are known to reduce the production of Th2 associated cytokine such as IL-4, IL-5 or IL10. The reference agent such as EtxB mutant (G33D) has an effect on GM1 mediated intracellular signaling events such as ADP-ribosyltransferase activity but no GM1 binding activity (See page 227, right column, last two paragraphs, in particular). The reference agent such as EtxB increases the expression of cytokines such as IL-2, and IFNγ that are known to decrease the expression of Th2 cytokine such as IL-4 that play a role in hypersensitivity condition. Nashar *et al.* further teach that the heat-labile enterotoxin of E coli (Etx) is a homologue of cholera toxin; the B subunits of the heat-labile enterotoxin of E coli (Etx) and cholera toxin (EtxB and CtxB) are nontoxic and have remarkably potent immunogenicity (See page 572, left column in particular).

The claimed invention in claim 24 differs from the teachings of the reference only by the recitation of said agent is capable of blocking an IgE mediated response.

The claimed invention in claim 26 differs from the teachings of the reference only by the recitation of said agent is capable of enhancing the production of IgG, IgA or mixtures thereof.

The claimed invention in claim 27 differs from the teachings of the reference only by the recitation of said agent reduces the production of Th2 associated cytokines.

The claimed invention in claim 30 differs from the teachings of the reference only by the recitation of said cytokines are IL-10 or TGFβ.

Yamamoto *et al.* teach an assay method for identifying agent such as mutant or derivative of cholera toxin (S61F and E112K) and heat labile toxin (LT) of E coli by measuring (1) a change in the antigen (Ova) specific IgE (See page 1204, right column, IgE analysis, in particular) (2) a change in the production of Th2 associated cytokines such as IL-4, IL-10 by ELISA (See page 1205, left column, Fig 3, in particular), (3) the effect of the agent on the GM1 mediated intracellular signaling events such as ADP-ribosyltransferase (See page 1204, right column, in particular), (4) measuring antigen specific T-cell reactivity such as T cell proliferation (See page 1207, Fig 2, page 1204, right column OVA- and CT-B specific CD4 T cell responses, in particular), (5) a change in antigen specific IgG levels (See page 1206, Fig 1, in particular). Yamamoto *et al* teach that antigen specific **IgE level for mutant S61F is reduced** (See page 1206, left column). Yamamoto *et al* further teach that the adjuvanicity of cholera toxin can be dissociated from the GM1 mediated intracellular signaling events such as ADP-ribosylatransferase activity and enterotoxicity using site directed mutagenesis to create mutant or derivative and measure various immune responses mentioned above (see page 1207, right column, in particular). Claim 24 is included in this rejection because once the levels of IgE are reduce, the IgE mediated response is essentially blocked by said mutant S61F.

Kim *et al.* teach agent such as a Cholera toxin (CT) and recombinant Cholera toxin B subunit CTB (CtxB), which is completely free of CTA, and the recombinant CtxB markedly increases the IgA response (See Fig 1, in particular) through the increase of cytokine such as TGFβ (See Table I, page 1203 second paragraph, Table IV, and Fig 4, in particular). Kim *et al* further teach that concentrations of CTB that significantly increased IgA production can also inhibit B cell growth and CTB has been used to **drown-regulated systemic immune responses** and to treat autoimmune disease (hypersensitivity condition) in animal models (See page 1203, right column, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cholera toxin B subunit (CTB) as taught by Kim *et al* or the

cholera toxin mutant (S61F and E112K) as taught by Yamamoto *et al* for the EtxB from the heat-labile enterotoxin of *E Coli* or the EtxB mutant (G33D) as taught by Nashar *et al.* for an assay method of identifying agent that is associated with induction of tolerance by down-regulate systemic immune responses as taught by Kim *et al* by measuring a reduction in antigen specific IgE levels as taught by Yamamoto et al or by measuring an increase in the IgA or TGFβ levels as taught by Kim *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One of ordinary skill in the art at the time the invention was made would have been motivated to identifying an agent for modulating hypersensitivity condition because Nashar *et al.* teach heat-labile enterotoxin of E coli (Etx) is a homolog of cholera toxin; the B subunits of (EtxB and CtxB) are nontoxic and have remarkedly potent immunogenicity (See page 572, left column in particular). Nashar *et al.* teach that agent such as EtxB mutant (G33D) has an effect on GM1 mediated intracellular signaling events such as ADP-ribosyltransferase activity but no GM1 binding activity (See page 227, right column, last two paragraphs, in particular) and yet causes an increase in the activation of CD4+ T cells, an increase in cytokines such as IL-2, IFNγ, an increase in the activation of CD4+ T cells, and no IL-4, IL-5 and IL-10 could be detected (See Fig 2, page 227, right column, last two paragraphs, in particular in particular). Yamamoto *et al* teach that the adjuvanicity of cholera toxin can be dissociated from the GM1 mediated intracellular signaling events such as ADP-ribosylatransferase activity and enterotoxicity using site directed mutagenesis to create mutant or derivative and measure the change in the production of Th2 associated cytokines such as IL-4, IL-10 by ELISA (See page 1205, left column, Fig 3, page 1207, right column, in particular). Kim *et al* teach that a significantly increase in IgA production can also inhibit B cell growth which is associated with oral tolerance and CTB has been used to **drown-regulated systemic immune responses** to treat autoimmune disease in animal models associated with high level of IL-4 T helper 2 cytokine (See page 1203, right column, in particular).

7. The following new grounds of rejection are necessitated by amendment filed 8/27/01.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "the agent" in claim 43 (a) has no antecedent base in the claim. Claim 43(a) requires "a mutant or derivative of EtxB" be contact with a ganglioside receptor.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 43-46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nashar *et al.* (of record Proc. Natl. Acad. Sci USA 93: 226-230, PTO 1449) in view of Yamamoto *et al.* (of record, J. Exp. Med. 185(7): 1203-1210, 1997, PTO 892) and Kim *et al* (of record, J Immunology 160: 1198-1203, 1998, PTO 892).

Nashar *et al.* teach an assay method for identifying an agent that modulates the immune response comprising contacting a mutant or derivative of EtxB such as G33D with a ganglioside receptor such as GM1 wherein the mutant or derivative is not coupled to an antigen (See page 227, Ezyme-linked Immunosorbent Assays (ELISAs, Fig 1, in particular). The reference assay involves in determining whether said mutant or derivative of EtxB (G33D) modulates a ganglioside associated activity by measuring a change in at least one parameter such as a change in IgG levels (See Fig 2) or a change in antigen specific T-cell reactivity (lymphocyte proliferation in the presence of EtxB or EtxB mutant (G33D) (See page 228, Table 1, Fig. 3, in

particular) or a change in the cytokine levels such as IL-2, IFNγ which are Th1 associated cytokines that are known to reduce the production of Th2 associated cytokine such as IL-4, IL-5 or IL10 or a change in IgA levels (See Fig 2, in particular). The reference EtxB mutant (G33D) has an effect on GM1 mediated intracellular signaling events such as ADP-ribosyltransferase activity but no GM1 binding activity (See page 227, right column, last two paragraphs, in particular). Nashar *et al.* teach heat-labile enterotoxin of E coli (Etx) is a homolog of cholera toxin; the B subunits of (EtxB and CtxB) are nontoxic and have remarkedly potent immunogenicity (See page 572, left column in particular).

The claimed invention in claim 44 differs from the teachings of the reference only by the recitation of said agent is capable of blocking an IgE mediated response.

The claimed invention in claim 45 differs from the teachings of the reference only by the recitation of said agent is capable of enhancing the production of IgG, IgA or mixtures thereof.

The claimed invention in claim 46 differs from the teachings of the reference only by the recitation of said agent reduces the production cytokine IL-4.

The claimed invention in claim 48 differs from the teachings of the reference only by the recitation of said agent increases the production cytokine TGFβ.

Yamamoto *et al.* teach an assay method for identifying agent such as mutant or derivative of cholera toxin (S61F and E112K) by measuring (1) a change in the antigen (Ova) specific IgE (See page 1204, right column, IgE analysis, in particular) (2) a change in the production of Th2 associated cytokines such as IL-4, IL-10 by ELISA (See page 1205, left column, Fig 3, in particular) wherein the antigen specific **IgE level for mutant S61F is reduced** (See page 1206, left column). Claim 44 is included in this rejection because once the levels of IgE are reduced; the reference mutant S61F essentially blocks the "IgE mediated response". The reference mutants such as S61F and E112K reduce the production of cytokine IL-4 (See page 1208, in particular). Yamamoto *et al* further teach that the adjuvanicity of cholera toxin can be dissociated from the GM1 mediated intracellular signaling events such as ADP-ribosyltransferase activity and enterotoxicity using site directed mutagenesis to create mutant or derivative and measure various immune responses as mentioned above (see page 1207, right column, in particular).

Kim *et al.* teach agent such as a Cholera toxin (CT) and recombinant Cholera toxin B subunit CTB (CtxB), which is completely free of CTA markedly, increased the IgA response (See Fig 1, in particular) through the increases in the expression of cytokine such as TGFβ (See Table I, page 1203 second paragraph, Table IV, and Fig 4, in particular). Kim *et al* further teach that

concentrations of CTB that significantly increased IgA production can also inhibit B cell growth and CTB has been used to **drown-regulated systemic immune responses** and to treat autoimmune disease, which is a hypersensitivity condition in animal models (See page 1203, right column, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure IgA response and TGFβ as taught by Kim *et al* or the decrease in IL-4 and IgE levels as taught by Yamamoto *et al* by contacting the EtxB mutant (G33D) to the ganglioside receptor such as GM1 as taught by Nashar *et al.* for an assay method of identifying agent that is associated with induction of tolerance by down-regulate systemic immune responses as taught by Kim et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One of ordinary skill in the art at the time the invention was made would have been motivated to identifying an agent for modulating hypersensitivity condition because Nashar *et al.* teach the heat-labile enterotoxin of E coli (Etx) is a homolog of cholera toxin; the B subunits of (EtxB and CtxB) are nontoxic and have remarkedly potent immunogenicity (See page 572, left column in particular). Nashar *et al.* teach that agent such as EtxB mutant (G33D) has an effect on GM1 mediated intracellular signaling events such as ADP-ribosyltransferase activity but no GM1 binding activity (See page 227, right column, last two paragraphs, in particular) and yet causes an increase in the activation of CD4+ T cells, an increase in cytokines such as IL-2, IFNγ which cause an increase in the activation of CD4+ T cells, and no IL-4, IL-5 and IL-10 could be detected (See Fig 2, page 227, right column, last two paragraphs, in particular in particular). Yamamoto *et al* teach that the adjuvanicity of cholera toxin can be dissociated from the GM1 mediated intracellular signaling events such as ADP-ribosylatransferase activity and enterotoxicity using site directed mutagenesis to create mutant or derivative and measure the change in the production of Th2 associated cytokines such as IL-4, IL-10 by ELISA (See page 1205, left column, Fig 3, page 1207, right column, in particular). Kim *et al* teach that a significantly increased in IgA production can also inhibit B cell growth which is associated with oral tolerance and CTB has been used to **drown-regulated systemic immune responses** and to treat autoimmune disease in animal models associated with hypersensitive condition (See page 1203, right column, in particular).

13. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nashar *et al.* (of record Proc. Natl. Acad. Sci USA 93: 226-230, PTO 1449) in view Yamamoto *et al.* (of record, J. Exp. Med. 185(7): 1203-1210, 1997, PTO 892) and Kim et al (of record, J Immunology 160: 1198-1203, 1998, PTO 892) as applied to claim 43 above and further in view of Okahashi et al (Infection and Immunity 64(5): 1516-1524; PTO 892).

The teachings of Nashar *et al*, Yamamoto *et al* and Kim *et al* have been discussed supra.

The claimed invention in claim 47 differs from the teachings of the references only by the recitation of said agent increases the production cytokine IL-10.

Okahashi *et al* teach Th1 cells selectively produce IL-2, gamma interferon and tumor necrosis factor beta, whereas Th2 cells are unique in the production of IL-4, IL-5, IL-6, IL-10 and IL-13. The Th1 cell subset is preferentially involved in cell mediated immunity and delayed type hypersensitivity while Th2 cells exhibit anti-inflammatory properties as well as providing help for B-cell response for certain IgG subclasses, IgE and IgA isotypes (See page 1516, in particular). Okahashi *et al* teach that oral immunization in mice with S typhimurium or cholera toxin B (CT-B) as adjuvant increases IL-10 accompanied by a decrease in IL-4 or IL-5 (See page 1519, Fig 4, page 1523, Fig 6, left column, in particular). Okahashi *et al* further teach that Th2-type cells which cannot produce IL-4 or IL-5 but which do produce IL-6 and IL-10 may play an important role in the induction of mucosal IgA response (See page 1524, left column, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure the increase in IL-10 as taught by Okahashi *et al* in addition to other Th2 cytokines as taught by Yamamoto by contacting the EtxB mutant (G33D) to the ganglioside receptor such as GM1 as taught by Nashar *et al.* for an assay method of identifying agent that is associated with induction of tolerance by down-regulate systemic immune responses as taught by Kim et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One of ordinary skill in the art at the time the invention was made would have been motivated to identifying an agent for modulating hypersensitivity condition because Nashar *et al.* teach the heat-labile enterotoxin of E coli (Etx) is a homologue of cholera toxin; the B subunits of (EtxB and CtxB) are nontoxic and have remarkably potent immunogenicity (See page 572, left column in particular). Nashar *et al.* teach that agent such as EtxB mutant (G33D) has an effect on GM1 mediated intracellular signaling events such as ADP-ribosyltransferase activity but no GM1

binding activity (See page 227, right column, last two paragraphs, in particular) and yet causes an increase in the activation of CD4+ T cells, an increase in cytokines such as IL-2, IFNγ which cause an increase in the activation of CD4+ T cells, and no IL-4, IL-5 and IL-10 could be detected (See Fig 2, page 227, right column, last two paragraphs, in particular in particular). Yamamoto *et al* teach that the adjuvanicity of cholera toxin can be dissociated from the GM1 mediated intracellular signaling events such as ADP-ribosyltransferase activity and enterotoxicity using site directed mutagenesis to create mutant or derivative and measure the change in the production of Th2 associated cytokines such as IL-4, IL-10 by ELISA (See page 1205, left column, Fig 3, page 1207, right column, in particular). Okahashi *et al* teach that Th2-type cells which cannot produce IL-4 or IL-5 but which do produce IL-6 and IL-10 may play an important role in the induction of mucosal IgA response (See page 1524, left column, in particular). Kim *et al* teach that a significantly increased in IgA production can also inhibit B cell growth which is associated with oral tolerance and CTB has been used to **drown-regulated systemic immune responses** and to treat autoimmune disease in animal models associated with hypersensitive condition (See page 1203, right column, in particular).

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
November 5, 2001

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